

AD_____

Award Number: DAMD17-99-1-9248

TITLE: Physiological Stress Reactivity and Breast Cancer

PRINCIPAL INVESTIGATOR: Pathik Wadhwa, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of California, Irvine
Irvine, CA 92668

REPORT DATE: October 2005

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.				
1. REPORT DATE 01/10/2005		2. REPORT TYPE FINAL		3. DATES COVERED (From - To) 1 Oct 1999 to 20 Sep 2005
4. TITLE AND SUBTITLE Physiological Stress Reactivity and Breast Cancer			5a. CONTRACT NUMBER	
			5b. GRANT NUMBER DAMD17-99-1-9248	
			5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Pathik Wadhwa, M.D., Ph.D.			5d. PROJECT NUMBER	
			5e. TASK NUMBER	
			5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of California, Irvine Irvine, CA 92668 E-Mail: pwadhwa@uci.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S)	
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT The objective of the present program of research is to study physiological processes that may mediate the links between psychological states and cancer. Specifically, the present study is designed to conduct an investigation of the cross-sectional associations between indices of stress reactivity and psychological coping styles in women with breast cancer and matched healthy controls. The aims of the project are: (1) To quantify parameters of biological reactivity to a behavioral stress paradigm in women with and without breast cancer; (2) To examine effects of menopause and familial risk on biological stress reactivity and emotional expression; and (3) To develop the methodology and obtain preliminary data which could justify subsequent, prospective research with high-risk populations. Data collection ended May 2005. Results of data analyses indicated significant differences in several cardiovascular indicators of stress-reactivity, as well as significant differences in changes in cortisol levels between the breast cancer and control group. While specific coping styles were shown to relate differently to cardiovascular stress responses and negative emotional responses among participants, coping styles were not associated with changes in cortisol levels. This suggests that the HPA-stress hormone link may not be mediated by perception of stress. Among reproductive and familial risk factors assessed, oral contraceptive use and length of use were associated with a dysregulated biological stress response profile (i.e., respond quicker and not recover as quickly). These results...				
15. SUBJECT TERMS breast cancer risk, stress, coping, behavior				
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT unlimited	18. NUMBER OF PAGES 8
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified		
			19b. TELEPHONE NUMBER (include area code) (949) 824-8238	

Table of Contents

Introduction.....	4
Body.....	4
Key Research Accomplishments.....	4
Reportable Outcomes.....	5
Conclusions.....	10
References.....	
Appendices.....	

INTRODUCTION:

The broad objective of the present program of research is to study physiological process that may mediate the links between psychological states and cancer. Specifically, the present study is designed to conduct an investigation of the cross-sectional associations between indices of stress reactivity and psychological coping styles in women with breast cancer and matched healthy controls. The aims of the project are: (1) To quantify parameters of biological reactivity to a behavioral stress paradigm in women with and without breast cancer; (2) To examine (a) group differences between women with and without breast cancer in biological stress reactivity, and (b) the effects of menopause and familial risk on biological stress reactivity and emotional expression; and (3) To develop the methodology and obtain preliminary data which could justify subsequent, prospective research with high-risk populations.

Body (Statement of Work):

- A. Recruitment and Assessment – Recruitment and assessment continued since the last reporting period and was concluded by May, 2005. During this time, 83 new participants have been recruited and assessed. This brings the final total number of participants to 118 (60 in Breast Cancer group and 58 in Health Control group).
- B. Database – All data, including clinical, sociodemographic, psychosocial, and physiological, have been entered using SPSS (11.5). Since the last reporting period, checks for accuracy and reliability and variability have been completed for the additional participants by July 2005.
- C. Hormone Assays – Biosamples (e.g., plasma and salivary cortisol) were collected, processed, and frozen at -80 degrees C for biochemical assays. Salivary cortisol assays for all participants have been performed and entered into the study database.
- D. Data Analyses – Preliminary (descriptive) data analyses of variables of interest were performed. Analyses that addressed the specific aims of the study were also conducted.

KEY RESEARCH ACCOMPLISHMENTS:

- A. Since the last report, the number of participants that have been assessed for the Breast Cancer (BC) group increased from 23 to 60, and the number of participants that have been assessed for the Healthy Control (HC) group increased from 12 to 58.
- B. We recruited and trained 2 additional research assistants to help with data collection due to staff turnover.

- C. We continued our recruiting effort by sending out letters to potential participants from the Breast Care Center and by sending out emails to faculty and staff of the UCI Medical Center.
- D. After data collection efforts ended, data was entered, checked for errors, and analyzed.
- E. Results from analyses will be used to complete a research article to be submitted for publication

REPORTABLE OUTCOMES:

I. Descriptive statistics of variables of interest

- A. Key socio-demographic characteristics of the participants (Breast Cancer (n = 60) and Healthy Control (n = 58)) are summarized in Table 1.

Table 1. Sample Characteristics by Group

Variables	BC Group	HC Group
Age	35-80 (<i>m</i> = 55)	34-84 (<i>m</i> = 53)
Ethnicity	15% Hispanic/Latino 75% Non-Hispanic White 7% Asian 3% Other	15% Hispanic/Latino 74% Non-Hispanic White 2% Asian 9% Other
Marital Status	70% married 15% widowed 15% single (incl. divorced)	50% married 2% widowed 48% single (incl. divorced)
Job Status	47% employed full time 12 % part time 15% homemaker 7% retired 8% unemployed	64% employed full time 14% part time 2 % homemaker 14% retired 7 % unemployed
Number of children	0-5 (<i>m</i> = 2)	0-7 (<i>m</i> = 2)
Level of school completed	7% High school grad 32 % some college 42% college 20% graduate training	2% some high school 5% high school grad 33% some college 18% college 30% graduate training
Annual household income	median = between \$70,000-\$80,000	median = between \$70,000-\$80,000
Other language besides English	28% spoke language other than English	28% spoke language other than English

B. Biological and familial risk factors of breast cancer are summarized in Table 2.

Table 2. Breast Cancer Risk Factors by Group

Variable	BC Group	HC Group
First menstrual period	10-15 ($m = 12$)	9-15 ($m = 12$)
Age of first pregnancy	16-39 ($m = 21$)	16-34 ($m = 20$)
Oral contraceptives used	Yes = 73%	Yes = 81%
Years of oral contraceptive use	.25-20 ($m = 5$)	.25-21 ($m = 5$)
Family History of BC (total # of relatives with BC)	0-11 ($m = 1.1$)	0-7 ($m = .76$)
Family history of cervical cancer	0-1 ($m = .12$)	0-1 ($m = .18$)
Family history of other cancers	0-6 ($m = 2.17$)	0-7 ($m = 1.79$)
HRT used	Yes 36.7%	51.7%
Years of HRT use	1-25 ($m = 7.48$)	.5-25 ($m = 7.75$)
Ever been pregnant	Yes = 87%	Yes = 83%
Age of BC diagnosis	32-78 ($m = 53$)	N/A
Body Mass Index	19.55-44.22 ($m = 26.57$)	18.82-43.79 ($m = 27.08$)

C. Distributions of Coping Styles based on the Marlowe Crown Social Desirability Scale (MCSD) and the Taylor Manifest Anxiety Scale (TMAS) among participants are summarized in Table 3.

Table 3. Coping Style by Group

Coping Styles	BC Group	HC Group
Repressive	30%	26%
Defensive	22%	19%
True low anxious	23%	21%
True high anxious	25%	31%

II. Results based on specific aims of study

A. Aim (1) To quantify parameters of biological reactivity to a behavioral stress paradigm in women with and without breast cancer

- The following table (Table 4) summarizes the cardiovascular parameters of stress-reactivity among women with and without breast cancer

Table 4. Cardiovascular Stress-Reactivity by Group

Variables	BC Group	HC Group
Heart rate – AUC (area under the curve)	5460-10573 (<i>m</i> = 7281.69)	4337-9807 (<i>m</i> = 6288.61)
Systolic Blood Pressure (SBP) – AUC	6843-16279 (<i>m</i> = 11161.41)	7685-14180 (<i>m</i> = 10492)
Diastolic Blood Pressure (DBP) – AUC	4595-10253 (<i>m</i> = 6652)	4739-8894 (<i>m</i> = 6280)
Mean Arterial Pressure (MAP)– AUC	5693-12617 (<i>m</i> = 8304)	6041-11158 (<i>m</i> = 7891)
Peak heart rate	69-137 (<i>m</i> = 102)	60-137 (<i>m</i> = 94)
% increase in heart rate from baseline to peak	3.33% - 45.95% (<i>m</i> = 26.48%)	2.5% - 47.11% (<i>m</i> = 26.43%)
% decrease in heart rate from peak to recovery	5.88% - 40.11% (<i>m</i> = 25.72%)	8.15% - 43.68% (<i>m</i> = 26.02%)
How long it takes to reach peak from baseline	38 - 81 min. (<i>m</i> = 48.21 min.)	35-68 min. (<i>m</i> = 45.16 min.)
How long it takes to return to recovery from peak	11 - 56 min. (<i>m</i> = 36.78 min.)	8 - 48 min. (<i>m</i> = 36.22 min.)

- The following table (Table 5) summarizes the neuroendocrine indicator of stress-reactivity (salivary cortisol) among women with and without breast cancer

Table 5. Neuroendocrine Stress-Reactivity by Group

Variable	BC Group	HC Group
Cortisol – AUC	2.07-103.01 (<i>m</i> = 37.06)	3.65-84.25 (<i>m</i> = 30.60)
Peak cortisol	.03-1.66 (<i>m</i> = .62)	.06-1.55 (<i>m</i> = .48)
% increase in cortisol from baseline to peak	-23.76% * - 94.64% (<i>m</i> = 61.22%)	-34.64%* - 93.11% (<i>m</i> = 43.79%)
% decrease in cortisol from peak to recovery	0** - 77.3% (<i>m</i> = 42.74%)	0** - 83.66% (<i>m</i> = 35.07%)
* Reactivity time from baseline to peak	21-105 min. (<i>m</i> = 50.26 min.)	19 - 100 min. (<i>m</i> = 49.95 min.)
* Reactivity time from peak to recovery	0 - 69 min. (<i>m</i> = 38.25 min.)	0 - 58 min. (<i>m</i> = 35.42 min.)

*some values actually decreased from baseline during the TSST

** 0 = no change meaning that the last reading or the “recovery value” is also the highest reading or the same as the “peak value”

- B. Aim (2a) To examine group differences between women with and without breast cancer in biological stress reactivity
- BC patients exhibited significantly greater stress-reactivity in cardiovascular and cortisol responses than HC participants.
 - For cardiovascular outcomes, BC participants have significantly higher heart rate area under the curve (AUC), higher peak heart rate, higher heart rate at the end of recovery, and took longer to reach peak from baseline values than HC participants
 - For cortisol outcomes, BC participants had significantly higher peak cortisol, greater % increase from baseline to peak in cortisol level, and greater % decrease from peak to recovery in salivary cortisol.
- C. Aim (2b) To examine the effects of menopause and familial risk on biological stress reactivity and emotional expression
- Bivariate correlations between breast cancer risk factors and outcome variables of interest (BC group only)
 - Biological and familial risk factors of breast cancer considered included: age of menarche, age of parity, years of oral contraceptive use, years of hormone replacement therapy (HRT) use, age, body mass index (BMI), family history of breast cancer, family history of cervical and ovarian cancer, and family history of other types of cancer

Cardiovascular Stress-Reactivity Parameters (heart rate, SBP, DBP, MAP)

- Greater number of years taking oral contraceptives is associated with
 - greater SBP Area under the curve, MAP area under the curve, greater MAP recovery value
 - lower % increase from baseline to peak in SBP, lower % decrease from peak to recovery value in SBP and MAP
 - greater reactivity time from baseline to peak CV values
 - slower reactivity time from peak to recovery CV values
- Greater age of cancer diagnosis is associated with
 - Greater SBP at peak and at recovery
 - Lower % increase from baseline to peak in heart rate and lower % decrease from peak to recovery value in heart rate
- Higher incidence of family history of breast cancer (total score of all relatives) is associated with
 - Lower SBP, DBP, and MAP peak values
 - Greater % decrease from peak to recovery in DBP
- Age of first pregnancy is associated with slower reactivity time from peak to baseline CV values
- Having used hormone replacement therapy (HRT) before (Y/N) is associated with greater peak SBP
- Having used oral contraceptives (Y/N) is associated with
 - greater reactivity time from baseline to peak CV values

- slower reactivity time from peak to recovery CV values

Neuroendocrine Stress-Reactivity Parameters (Cortisol)

- Greater number of years using oral contraceptives is associated with greater baseline cortisol
- Having used oral contraceptives is associated with greater time from baseline to peak in salivary cortisol

Emotional Stress-Reactivity Response (Negative Affect)

- There were no significant associations between family and reproductive risk factor of breast cancer and negative affect

D. Aim (3) To develop the methodology and obtain preliminary data which could justify subsequent, prospective research with high-risk populations

- Analyses that examined differences in psychological coping styles and physiological stress-reactivity responses between breast cancer survivors and a healthy control group produced some interesting results that warrant further research with high-risk populations
 - Specifically, results showed that people who are characteristically repressive copers were more likely to have higher % increase in heart rate from baseline to peak and significantly higher % decrease in heart rate from peak to baseline than those who are characteristically defensive and highly anxious copers.
 - Even though there were no significant differences in cortisol based on repressive and non-repressive coping styles, there were interesting group differences in negative affect based on coping styles
 - Specifically, repressive copers had significantly lower peak negative affect (NA), higher % increase from baseline to peak in NA, and greater area under the curve for NA than defensive copers
- In addition, analyses of the type of strategies breast cancer patients used to regulate their emotions during the behavioral challenge were significantly related to physiological and emotional stress-reactivity.
 - Specifically, the greater use of attention deployment (e.g., distraction) was significantly associated with greater cardiovascular, neuroendocrine, and negative emotional stress-reactivity than lesser use of attention deployment
 - The greater use of humor (e.g., make light of situation) was significantly associated with lower neuroendocrine and negative emotional stress-reactivity than lesser use of humor

CONCLUSIONS:

- As expected, survivors of breast cancer exhibited greater cardiovascular and neuroendocrine stress-reactivity than women who have not had breast cancer in response to a standardized laboratory behavioral task
- Among biological and familial risk factors of breast cancer, the use of oral contraceptives and the number of years of oral contraceptives were significantly associated with physiological stress reactivity parameters
- However, none of the biological and familial risk factors were associated with negative emotional response to the behavioral challenge
- Results also provided preliminary evidence that psychological coping styles and strategies were important predictors of physiological stress-reactivity responses
- However, there were no significant group differences in psychological coping styles between breast cancer and healthy control group in the current study
- Lack of power to detect effects due to small sample size may contribute to lack of differences between groups